Ranibizumab and Aflibercept for the Treatment of Pigment Epithelial Detachment in Neovascular Age-Related Macular Degeneration: Data from an Observational Study

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Abstract: Purpose: To assess the effect of intravitreal ranibizumab and aflibercept on retinal pigment epithelial detachment (RPED) in patients with neovascular age-related macular degeneration. Methods: This was a retrospective analysis of data from a prospectively designed and implemented clinical audit. Analysis included change in RPED dimensions and visual acuity in 92/233 treatment-naive eyes with neovascular age-related macular degeneration and RPED 6 months after treatment with either aflibercept or ranibizumab. Results: There was no significant between-group difference in the adjusted mean change for maximum RPED height (P = 0.195), diameter (P = 0.522) or visual acuity (P = 0.836) at 6 months. Injection frequency was the only clinical variable that affected RPED height (P = 0.050) and visual acuity change for both treatment groups (P = 0.004). Around 30% of eyes in each group had complete resolution of RPED at 6 months. Conclusion: Eyes with neovascular age-related macular degeneration and RPED showed significant functional and anatomical responses after 6 months of intravitreal anti–vascular endothelial growth factor injections. However, we found no significant difference in anatomical response or change in visual acuity between eyes treated with ranibizumab compared with aflibercept. Larger, prospectively designed, randomized studies with longer term follow-up may identify a difference between the two drugs that we did not detect.

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RANIBIZUMAB AND AFLIBERCEPT FOR THE TREATMENT OF PIGMENT EPITHELIAL DETACHMENT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Data from an Observational Study

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Purpose: To assess the effect of intravitreal ranibizumab and aflibercept on retinal pigment epithelial detachment (RPED) in patients with neovascular age-related macular degeneration.

Methods: This was a retrospective analysis of data from a prospectively designed and implemented clinical audit. Analysis included change in RPED dimensions and visual acuity in 92/233 treatment-naive eyes with neovascular age-related macular degeneration and RPED 6 months after treatment with either aflibercept or ranibizumab.

Results: There was no significant between-group difference in the adjusted mean change for maximum RPED height (P = 0.195), diameter (P = 0.522) or visual acuity (P = 0.836) at 6 months. Injection frequency was the only clinical variable that affected RPED height (P = 0.050) and visual acuity change for both treatment groups (P = 0.004). Around 30% of eyes in each group had complete resolution of RPED at 6 months.

Conclusion: Eyes with neovascular age-related macular degeneration and RPED showed significant functional and anatomical responses after 6 months of intravitreal anti–vascular endothelial growth factor injections. However, we found no significant difference in anatomical response or change in visual acuity between eyes treated with ranibizumab compared with aflibercept. Larger, prospectively designed, randomized studies with longer term follow-up may identify a difference between the two drugs that we did not detect.

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Retinal pigment epithelial detachment (RPED) from the underlying Bruch membrane is a well-known feature of neovascular age-related macular degeneration (nAMD). Its pathophysiology is however poorly understood and treatment can be challenging.[1] Vascularized RPEDs occur in conjunction with choroidal neovascularization with fibrovascular material or hemorrhage accumulating within the RPED.[2]

Rips can complicate vascularized RPEDs,[3] and subfoveal RPEDs have been associated with a worse visual prognosis.[4] Previous studies have shown that RPEDs in nAMD respond poorly to most treatments including photodynamic therapy.[5] Anti–vascular endothelial growth factor (VEGF) agents have shown variable responses.[5–10] Spectral domain optical coherence tomography (SD-OCT) has been used to identify and provide more detailed anatomical assessment of RPEDs. These have been defined as "any separation of RPE from Bruch membrane as seen on SD-OCT" and their reflective properties have been shown to predict their response to anti-VEGF therapy.[11]

Ranibizumab and aflibercept are the two most common anti-VEGF drugs for the treatment of nAMD. Although VEGF-A, a member of the VEGF family, is

the key player in the pathogenesis of nAMD, there is some evidence that placental growth factor (PlGF, another member of the VEGF family) may also be implicated in the pathogenesis of choroidal neovascularization.[12] Hence, because of different pharmacological characteristics, ranibizumab and aflibercept may have different treatment responses in specific subgroups. Although ranibizumab acts as antibody against all isoforms of VEGF-A, the decoy-receptor action of aflibercept allows for binding and thus blocking of not only VEGF-A but also VEGF-B and placenta induced growth factor.[13]

To date, there is limited information on the comparative efficacy of ranibizumab and aflibercept in terms of RPED resolution, RPE tear rates, and visual acuity (VA) improvement in nAMD eyes with RPED. The aim of this study was to study the effect of intravitreal ranibizumab and aflibercept on these RPED dimensions after 6 months of treatment in patients with nAMD.

Methods

This was a retrospective analysis of data from a prospectively designed and implemented clinical audit[14] performed in four centers: three in Sydney, Australia, and 1 in Zurich, Switzerland. The study was approved by the South Eastern Sydney Local Health District, the Ethics Committee of the Canton of Zurich, and performed in accordance with the ethical standards of the Declaration of Helsinki.

We identified a consecutive case series of treatment-naive patients with nAMD with RPED who started treatment with either aflibercept or ranibizumab from October 1, 2013 (the date from which aflibercept was used in the above centers), until November 1, 2015. The Fight Retinal Blindness! database, the details of which have been published previously,[14] was used to identify patients. Patients who had been diagnosed with idiopathic polypoidal choroidal vasculopathy or retinal angiomatous proliferation or who had received other adjuvant treatment modalities in the study eye such as photodynamic therapy after the start of anti-VEGF therapy were automatically excluded during the database analysis. A retinal specialist (A.V.) examined the baseline OCTs of all eyes and thus identified the inclusion criteria, which were as follows: presence of RPED at baseline defined as "any separation of RPE from Bruch membrane as seen on SD-OCT" that was not drusenoid within the central 6 × 6 cube; presence of a follow-up OCT on or after 22 weeks; OCT images of sufficient quality at both baseline and follow-up to allow analysis; and eyes having monotherapy with either aflibercept or ranibizumab throughout the 6 months of follow-up. Exclusion criteria were poor image quality, presence of pigment epithelial tear at baseline, polypoidal choroidal vasculopathy, or any other confounding retinopathies or use of other adjuvant treatment modalities in the study eye such as photodynamic therapy/laser after the start of anti-VEGF therapy.

Baseline examination and 6 months follow-up visits included evaluation of VA measured on a standard logarithm of the minimal angle of resolution chart, with their current spectacles if worn and pin hole, with the highest value entered. An ophthalmic examination included dilated fundoscopy, SD-OCT, and fluorescein angiography; the last was usually performed only at baseline on all cases. Treatments were given completely at the discretion of the practitioner in consultation with their patient, thereby reflecting real-world practice.

The assessment was performed by an independent reading center (Singapore Eye Research Institute) masked to the treatment arms. SD-OCT was used to examine the maximum RPED dimensions at baseline and after 6 months of treatment (first OCT after 22 weeks). OCT with cube examination was performed using either the Spectralis (Heidelberg Engineering, Heidelberg, Germany) or Cirrus (Carl Zeiss Meditec, Inc, Oberkochen, Germany), and the same machine was used at baseline and at 6 months. The following data were recorded, with the grader being masked for drug type, using the caliper provided by the manufacturer's software: maximum RPED height (vertical distance from Bruch membrane to the RPE border) and maximum horizontal diameter of RPE elevation. Manual adjustment of the segmentation line was performed where required. Retinal pigment epithelial detachments were graded as hollow, solid, or mixed based on their SD-OCT reflectivity at baseline according to the method previously described by Punjabi et al.[11] Spectral domain optical coherence tomography at baseline was also used to classify them into subfoveal, juxtafoveal, or extrafoveal depending on the location (subfoveal—RPED is under the center of the foveal

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depression, juxtafoveal—if RPED lies in an area 1 μm–250 μm from the fovea, extrafoveal—if the RPED lies beyond 250 μm from the center or the fovea).

Our primary outcome measure was the change in RPED dimensions (maximum RPED height and maximum horizontal diameter) in micrometers after 6 months of treatment in each group. The secondary outcome measure was the change of VA at 6 months.

Descriptive statistics included the mean, SD, median, interquartile range, and percentages where appropriate. Baseline characteristics were compared between treatment arms using Student *t*, Wilcoxon rank-sum, chi-square, and Fisher tests where appropriate. Comparison of RPED and VA outcomes at 6 months between the groups receiving ranibizumab or aflibercept was analyzed using regression models, with the change in RPED height, RPED diameter, and the change in VA as the outcome variables, treatment arm as the primary predictor variable, adjusted for baseline age, baseline RPED dimensions, and VA. Appropriate conversion formulae were used to make measurement adjustments in tabulating aggregate results generated by different OCT (Cirrus and Spectralis) machines before performing statistical calculations.[15] Clinical characteristics including injection frequency within the 6 months of treatment, angiographic size and subtype at baseline, and RPED reflectivity (hollow, mixed, or solid) and location on SD-OCT (extrafoveal, juxtafoveal, or subfoveal) at baseline were also included in the regression model and their effects on RPED outcomes investigated. These models were also used to estimate adjusted (least squares) mean values correcting for differences in baseline characteristics between treatment groups. Within-group change in RPED and VA outcomes were analyzed using paired *t* tests. The number of injections and visits were compared by a Poisson regression model with an offset for log days follow-up. Tests for proportions were compared using the chi-square test where appropriate. Correlations between injection frequency and change in RPED dimensions and VA were analyzed using Pearson correlations (r). A $P < 0.05$ was considered statistically significant. All analyses were performed using R version 3.2.4.[16]

Results

We identified 233 eyes from 215 patients beginning monotherapy treatment with ranibizumab or aflibercept at the four centers. The 97/233 (42%) eyes with RPED that met eligibility criteria were graded by the reading center. Of these 97 eyes, 63 (65%) were also part of a previous study comparing 12-month visual outcomes for ranibizumab and aflibercept.[17] Retinal pigment epithelial detachment dimensions for five eyes were marked as ungradable because of poor image quality at either 1 or both visits and were excluded from the analysis. Statistical analyses are thus based on 92 eyes. From previously published data, we estimated that the rate of eyes switching therapy in the first 6 months of treatment was 11.7% for ranibizumab to aflibercept and 2.6% from aflibercept to ranibizumab. Noncompletion rates were estimated to be similar in the first 6 months of treatments (10.7% for both drugs and these rates are for the overall cohort of exudative AMD).[17] The treatment strategy was treat and extend for all the centers included with 82.8% and 81.3% of the visits being injection visits for ranibizumab and aflibercept, respectively. A majority of eyes were examined using the Spectralis SD-OCT machine (Table 1); thus all measurements were converted to Spectralis measurements.

Demographic Characteristics

The demographic characteristics for the 92 patients included in the analysis are summarized in Table 1. Patients treated with ranibizumab were significantly older than aflibercept-treated patients (84.1 years vs. 78.2 years, $P < 0.001$). Those treated with aflibercept had a mean larger maximum RPED diameter compared with ranibizumab (2,170 μm vs. 1,735 μm, $P = 0.033$), although maximum RPED height was similar between the 2 groups (230 μm vs. 263 μm, for ranibizumab for aflibercept, respectively; $P = 0.242$). There were more extrafoveal and juxtafoveal RPEDs in ranibizumab-treated patients, whereas aflibercept-treated patients had more subfoveal RPEDs ($P = 0.047$). Ranibizumab-treated patients also had more predominantly classic lesions, whereas aflibercept-treated patients had more occult lesions ($P = 0.045$).

Retinal Pigment Epithelial Detachment Outcomes at 6 Months

Outcomes at 6 months for the ranibizumab and aflibercept treatment arms are summarized in Table 2. There was no significant between-group difference ($P > 0.05$) in the adjusted mean change {mean (95% confidence interval [CI])} for maximum RPED height at 6 months for ranibizumab (−107.9 μm [−157.3, −58.4]) and aflibercept (−69.6 μm [−116.5, −22.6]), although both groups recorded significant within-group changes ($P < 0.001$ for both treatment groups). Within-group change (mean [95% CI]) in maximum RPED height for PED types in both treatment groups combined was significant for hollow (−129.7 μm [−172.1, −87.2] $P < 0.001$) and solid

Table 1. Comparison of Baseline Demographic Characteristics of Patients With PED at Baseline Between Treatment Arms

	Ranibizumab	Aflibercept	*P*
No. of patients	42	50	
Baseline age, years, mean (SD)	84.1 (6.4)	78.2 (8.0)	<0.001
Female (%)	67	62	0.805
Left eye (%)	38	52	
Baseline VA (letters), mean (SD), (approximate Snellen equivalent)	63.1 (20.4), (20/50−)	57.8 (19.8), (20/63−)	0.210
Baseline maximum RPED height, mean (SD), microns	230.0 (107.2)	262.6 (156.8)	0.242
Baseline maximum RPED diameter, mean (SD), microns	1,734.6 (895.4)	2,170.4 (1,009.2)	0.033
RPED reflectivity, n (%)			
Hollow	23 (55)	26 (52)	0.491
Mixed	4 (10)	9 (18)	
Solid	15 (36)	15 (30)	
Location of RPED on SD-OCT, n (%)			
Extrafoveal	13 (31)	10 (20)	0.047
Juxtafoveal	11 (26)	6 (12)	
Subfoveal	18 (43)	34 (68)	
Baseline greatest linear dimension, median (interquartile range)	2,561 (1,958–3,557)	3,122 (1,863–4,402)	0.267
Angiographic subtype, n (%)			
Occult	25 (60)	39 (78)	0.045
Minimally classic	4 (10)	3 (6)	
Predominantly classic	11 (26)	4 (8)	
Unknown	2 (5)	4 (8)	
SD-OCT machine, n (%)			
Cirrus	23 (55)	16 (32)	0.047
Spectralis	19 (45)	34 (68)	

PEDs (−67.8 μm [−111.7, −23.8]; $P = 0.004$) but not mixed PEDs (−68.5 [−139.3, 2.3]; $P = 0.057$). Injection frequency was the only clinical variable to have a significant impact on RPED height ($P = 0.050$), with a weak correlation between more frequent injections and greater reductions in RPED height (r = −0.17; $P = 0.097$). Thirty-one of 92 patients (34%) had complete resolution of PED at 6 months (40% for ranibizumab vs. 28% for aflibercept; $P = 0.299$). None of the baseline characteristics had a statistically significant impact on the complete resolution of RPED (Table 3).

The adjusted mean change (95% CI) in maximum RPED diameter was −634.8 μm (−1,082.9, −186.6) for ranibizumab and −462.6 μm (−890.2, −35.0) for aflibercept ($P = 0.522$). Within-group changes in maximum RPED diameter were statistically significant for both ranibizumab ($P = 0.002$) and aflibercept ($P < 0.001$). Within-group change (mean [95% CI]) in maximum RPED height for PED types in both treatment groups combined was significant for hollow (−623.0 μm [−953.6, −292.4]; $P < 0.001$) and solid PEDs (−554.9 μm [−915.1, −194.7]; $P = 0.004$) but not mixed PEDs (−614.1 [−1,354.0, 125.9]; $P = 0.096$). There were no significant predictors of maximum RPED diameter change at 6 months.

Visual Acuity Outcomes at 6 Months

The adjusted mean improvement (95% CI) in VA was 6.5 letters (2.6, 10.4) for ranibizumab and 7.0 letters (3.3, 10.7) for aflibercept, with no significant difference between the 2 treatments ($P = 0.836$). Within-group change in VA was significant for both ranibizumab ($P = 0.002$) and aflibercept ($P < 0.001$). Injection frequency was the only clinical variable to have a significant impact on VA change for both treatment groups ($P = 0.004$) with more frequent injections correlated with greater gains in VA (r = 0.26; $P = 0.012$).

Injections and Visits

The mean number of injections (4.7 vs. 4.9; $P = 0.862$) and visits (5.1 vs. 5.3; $P = 0.855$) did not differ between ranibizumab- and aflibercept-treated patients.

Adverse Events

Only 2 eyes were recorded as developing an RPE tear within the 6-month follow-up period; 1 was treated with ranibizumab and the other with aflibercept.

Table 2. Comparison of Outcomes at 6 Months Between Treatment Arms and Resulting *P* values

	Ranibizumab	Aflibercept	*P*
No. of eyes	42	50	
PED resolved, n (%)	17 (40)	14 (28)	0.299
Maximum RPED height			
Baseline (SD)	230.0 (107.2)	262.6 (156.8)	
Final (SD)	134.2 (132.3)	157.5 (153.3)	
Δ (95% CI)	−95.8 (−133.2 to −58.4)	−105.1 (−147.8 to −62.3)	
Adjusted Δ (95% CI)	−107.9 (−157.3 to −58.4)	−69.6 (−116.5 to −22.6)	0.195
Maximum RPED diameter			
Baseline (SD)	1,734.6 (895.4)	2,170.4 (1,009.2)	
Final (SD)	1,194.1 (1,256.8)	1,520.2 (1,328.6)	
Δ (95% CI)	−540.6 (−872.9 to −208.3)	−650.1 (−968.5 to −331.8)	
Adjusted Δ (95% CI)	−634.8 (−1,082.9 to −186.6)	−462.6 (−890.2 to −35.0)	0.522
BCVA			
Baseline (SD), (approximate Snellen equivalent)	63.1 (20.4), (20/50−)	57.8 (19.8), (20/63−)	
Final (SD), (approximate Snellen equivalent)	68.4 (22.4), (20/40−)	66.3 (15.4), (20/50+)	
Δ (95% CI)	5.3 (2.1 to 8.5)	8.5 (5.2 to 11.9)	
Adjusted Δ (95% CI)	6.5 (2.6 to 10.4)	7.0 (3.3 to 10.7)	0.836
Injections (range)	4.7 (1 to 7)	4.9 (1 to 7)	0.862
Visits (range)	5.1 (2 to 7)	5.3 (2 to 7)	0.855

Adjusted ΔRPED and ΔBCVA outcomes are the least-squared mean values after adjusting for differences in baseline characteristics between the treatment groups.

BCVA, best-corrected visual acuity.

Discussion

In this study, we found that treatment-naive eyes with nAMD and RPED showed significant anatomical and functional responses to intravitreal anti-VEGF injections of either ranibizumab or aflibercept after 6 months of treatment. Injection frequency was the only variable found to have a significant impact on RPED height, with a weak correlation between more frequent injections and greater reductions in RPED height and diameter. More frequent injections were also found to have greater gains in VA. However, we did not find significant differences between the two drugs in either anatomical or functional outcomes. We found complete resolution of RPED in 42% cases. Neither the drug type nor any baseline characteristic independently predicted the complete resolution of eyes with RPED or improved VA.

We used regression analysis to estimate event rates in the primary analysis to account for the baseline differences between the two groups. Eyes receiving ranibizumab were significantly older (mean 82 years vs. 78 years), had somewhat smaller lesions (1,735 μm vs. 2,170 μm diameter), were more likely to be extrafoveal, and have a classic component. The difference in age is likely because of concerns expressed soon after aflibercept had been approved that it might confer a higher risk of thromboembolic events.[18] Larger lesions might point to aflibercept being used for more advanced lesions, although its greater use for occult lesions may not be consistent with this.

Previous studies have reported the response of anti-VEGF treatment in patients with nAMD with RPED. The CATT subanalysis identified total foveal thickness and retinal pigment epithelium elevation on time-domain OCT as baseline anatomical predictors of VA outcomes at month 12.[4] However, RPEDs were not identified as significant covariates for treatment response in a subanalysis of HARBOR.[19] Ach et al[7] previously showed a nonsignificant decrease in PED height with bevacizumab for vascularized RPEDs over a period of 9 months (mean height decrease: 81.7 μm, $P > 0.05$; follow-up 37.9 ± 18.3 weeks). The VIEW 1 and 2 trials of nAMD reported that patients treated with aflibercept had higher rates of RPED flattening than those treated with ranibizumab (Shah CP, et al. AAO 2013; Poster PA088). Differences between our findings and previous work could be attributed to the use of different drugs, measurement techniques (SD-OCT was used in HARBOR and time-domain OCT was used in CATT), treatment protocols, and small sample sizes. In studies of treatment-naive vascularized RPEDs, Panos et al[10] observed a reduction in mean PED height of 135 μm after pro re nata ranibizumab for 12 months; their results were not dissimilar to those presented here (unadjusted mean of 96 μm for ranibizumab, 105 μm for aflibercept).

Other studies have reported the effect of switching treatment from ranibizumab to aflibercept on RPEDs.

Table 3. Summary of Characteristics of Eyes That Had Complete Resolution of PED Compared With Those That Did Not

	Resolved	Unresolved	*P*
No. of patients	31	61	
Treatment arm, n (%)			
Ranibizumab	17 (55)	25 (41)	0.299
Aflibercept	14 (45)	36 (59)	
Baseline age, mean (SD)	80.0 (7.5)	81.3 (8.1)	0.452
Female (%)	61	66	0.861
Baseline VA, mean (SD), (approximate Snellen equivalent)	65.0 (17.2), (20/50)	57.8 (21.2), (20/63−)	0.086
VA change, mean (95% CI)	8.4 (5.0–11.8)	6.4 (3.3–9.4)	0.371
Baseline maximum RPED height, mean (SD)	262.9 (103.0)	240.0 (151.2)	0.395
Baseline maximum RPED diameter, mean (SD)	1,772.0 (842.2)	2,064.6 (1,031.0)	0.155
RPED reflectivity, n (%)			
Hollow	17 (55)	32 (52)	1.000
Mixed	4 (13)	9 (15)	
Solid	10 (32)	20 (33)	
Location on SD-OCT, n (%)			
Extrafoveal	10 (32)	13 (21)	0.460
Juxtafoveal	6 (19)	11 (18)	
Subfoveal	15 (48)	37 (31)	
Baseline GLD, median (interquartile range)	2,656 (2,025, 4,168)	2,824 (1,936, 4,100)	0.882
Angiographic subtype, n (%)			
Occult	22 (71)	42 (69)	0.582
Minimally classic	1 (3)	6 (10)	
Predominantly classic	6 (19)	9 (15)	
Unknown	2 (6)	4 (7)	

Kumar et al reported the results of switching treatments in a group of eyes with nAMD, 97% of which had RPED.[20] They found a significant change in maximum RPED height and central retinal thickness 3 months after switching from ranibizumab to aflibercept but no change in VA. In a small case series, Patel et al reported dramatic resolution of RPEDs after switching from ranibizumab to aflibercept.[5] However, these studies were case series with sample sizes as small as 34 and 3 eyes. Chan et al, in a retrospective study of 189 eyes that switched to aflibercept from either ranibizumab or bevacizumab or mixed treatment have reported improved anatomical and functional outcomes 6 months after transition. However, the more robust response in the eyes with PED (n = 102) as compared to eyes without PED was thought to be due to a relative ceiling effect of certain OCT variables in eyes without PED because subretinal fluid height and volume was substantially lower in eyes without PED than in eyes with PED.[21] Broadhead et al recently reported that aflibercept was effective in reducing RPED size in previously treatment-resistant patients who were treated with ranibizumab. However, similar to other studies, reduction in RPED size did not correlate with improved VA in their study.[8]

A recent study by Dirani et al is one of the few reports of the comparative efficacy of ranibizumab and aflibercept on RPEDs associated with newly diagnosed nAMD. They studied the effect of three injections of either drug on these patient and reported significant anatomical and functional responses to intravitreal anti-VEGF injections of either ranibizumab or aflibercept.[22] Multivariate analysis revealed that VA improvement was associated with lower VA at baseline ($P = 0.001$) and the presence of subretinal fluid ($P = 0.001$). The degree of RPED reduction was associated with RPED height at baseline ($P = 0.001$), predominantly serous RPEDs ($P = 0.003$), and use of aflibercept ($P = 0.022$). As in this study, drug type was not associated with change in VA at 3 months in this study.

We studied the effect of these two drugs on treatment-naive nAMD eyes with RPED 6 months after starting treatment. Because RPEDs generally require prolonged anti-VEGF treatment for optimal response,[6,7,10] we studied 6-month outcomes of the 2 anti-VEGF drugs rather than just the loading phase of 3 injections. Similar to the study by Dirani et al, our study found a significant reduction in RPED dimensions with both ranibizumab and aflibercept treatment. However, our study did not find a stronger effect of aflibercept on flattening of the RPED as reported by other studies.[22,23]

Previous studies have suggested that RPED type based on its OCT reflectivity may be an important characteristic that predicts response to therapy.[8,9,11,22] We also found that hollow RPEDs responded better to anti-VEGF treatment. However, there was no statistically significant difference in the effect of the two treatments on RPED dimensions or VA outcomes. We found good VA improvement regardless of the drug type, similar to other studies.[22] None of the other baseline characteristics seemed to have any influence on the functional outcomes in our study. However, previous studies have suggested that functional long-term prognosis of RPED is generally poor, even with anti-VEGF therapy.[24,25] Vascularized RPEDs and baseline RPED height have been reported to be associated with poor functional outcomes,[26–28] but we have not replicated this finding in this 6-month study.

Our study has several limitations. Numbers were not large, at around 50 eyes per group: it is possible that a larger study may have found significant differences between groups that were not apparent in this study. We cannot exclude the possibility that clinicians chose a certain drug for a specific clinical presentation of RPED. Personal preference and previous experience with either of the drugs may have influenced treatment choices in such cases, for example aflibercept may have been used in cases with more advanced RPEDs. The significantly larger greatest linear diameter of eyes that were treated with aflibercept may be evidence of this, although the difference was not very large. Retinal pigment epithelial detachment dimensions were assessed using maximum RPED height and width as surrogate markers, as have most previous studies.[5,7,8,11] Although quantitative changes in RPED volume using SD-OCT automated software have been proposed as a predictor of RPED response,[29] the automated "RPED elevation" software shows poor agreement with manual measurements becauseof a high rate of segmentation line breakdown.[30] Hence, further development of software to analyze RPED morphology better is needed to ensure more accurate quantification of RPEDs. One other potential limitation was the short follow-up duration in this study. This analysis included only patients who completed 6 months of monotherapy and could have overestimated the outcome in eyes with RPED. Based on previous analyses,[17] switching rates were low but biased in favor of ranibizumab to aflibercept switching, whereas noncompletion rates were similar between the two drugs. Studies among patients having PED with long-term follow-up are necessary to confirm our results. Also, we cannot rule out the possibility of an asymmetrical distribution of idiopathic polypoidal choroidal vasculopathy between both drug groups because of the lack of routine performance of indocyanine green angiography reflecting the real-world practice in the studied population, but it is likely not a an important confounding factor given the fact that idiopathic polypoidal choroidal vasculopathy is an uncommon type of neovascular lesion in the studied population.

In conclusion, treatment-naive patients with nAMD and RPED showed significant anatomical and functional improvements at 6 months with both intravitreal ranibizumab or aflibercept injections. Injection frequency was the only variable that had a significant impact on the anatomical response, especially on RPED height and VA outcomes. There was no significant difference between the two drugs in anatomical response in terms of reduction in RPED height and width or functional response. Larger and prospectively designed studies with longer term follow-up may be needed to understand better the influence of baseline characteristics and whether there is a difference in treatment responses between the two drugs.

Key words: age-related macular degeneration, vascular endothelial growth factor inhibitors, retinal pigment epithelial detachment.

References

1. Clemens CR, Krohne TU, Charbel Issa P, et al. High-resolution optical coherence tomography of subpigment epithelial structures in patients with pigment epithelium detachment secondary to age-related macular degeneration. Br J Ophthalmol 2012;96:1088–1091.
2. Mrejen S, Sarraf D, Mukkamala SK, Freund KB. Multimodal imaging of pigment epithelial detachment: a guide to evaluation. Retina 2013;33:1735–1762.
3. Doguizi S, Ozdek S. Pigment epithelial tears associated with anti-VEGF therapy: incidence, long-term visual outcome, and relationship with pigment epithelial detachment in age-related macular degeneration. Retina 2014;34:1156–1162.
4. Ying GS, Huang J, Maguire MG, et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2013;120:122–129.
5. Patel KH, Chow CC, Rathod R, et al. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. Eye (Lond) 2013;27:663–667; quiz 8.
6. Parodi MB, Iacono P, Papayannis A, et al. Intravitreal ranibizumab for pigment epithelium detachment with subfoveal occult choroidal neovascularization: a prospective 24-month case series. Am J Ophthalmol 2013;155:103–108.e2.
7. Ach T, Hoeh AE, Ruppenstein M, et al. Intravitreal bevacizumab in vascular pigment epithelium detachment as a result of subfoveal occult choroidal neovascularization in age-related macular degeneration. Retina 2010;30:1420–1425.
8. Broadhead GK, Hong T, Zhu M, et al. Response of pigment epithelial detachments to intravitreal aflibercept among patients

with treatment-resistant neovascular age-related macular degeneration. Retina 2015;35:975–981.
9. Arora S, McKibbin M. One-year outcome after intravitreal ranibizumab for large, serous pigment epithelial detachment secondary to age-related macular degeneration. Eye (Lond) 2011;25:1034–1038.
10. Panos GD, Gatzioufas Z, Petropoulos IK, et al. Effect of ranibizumab on serous and vascular pigment epithelial detachments associated with exudative age-related macular degeneration. Drug Des Devel Ther 2013;7:565–569.
11. Punjabi OS, Huang J, Rodriguez L, et al. Imaging characteristics of neovascular pigment epithelial detachments and their response to anti-vascular endothelial growth factor therapy. Br J Ophthalmol 2013;97:1024–1031.
12. Rakic JM, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. Invest Ophthalmol Vis Sci 2003;44:3186–3193.
13. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis 2012;15:171–185.
14. Gillies MC, Walton R, Simpson JM, et al. Prospective audit of exudative age-related macular degeneration: 12-month outcomes in treatment-naive eyes. Invest Ophthalmol Vis Sci 2013;54:5754–5760.
15. Diabetic Retinopathy Clinical Research Network Writing C; Bressler SB, Edwards AR, Chalam KV, et al. Reproducibility of spectral-domain optical coherence tomography retinal thickness measurements and conversion to equivalent time-domain metrics in diabetic macular edema. JAMA Ophthalmol 2014; 132:1113–1122.
16. Frampton JE. Crizotinib: a review of its use in the treatment of anaplastic lymphoma kinase-positive, advanced non-small cell lung cancer. Drugs 2013;73:2031–2051.
17. Gillies MC, Nguyen V, Daien V, et al. Twelve-month outcomes of ranibizumab vs. aflibercept for neovascular age-related macular degeneration: data from an observational study. Ophthalmology 2016;123:2545–2553.
18. Beaumont PE, Petocz P, Kang HK. Is there risk of stroke with aflibercept? Ophthalmology 2014;121:e4.
19. Regillo CD, Busbee BG, Ho AC, et al. Baseline predictors of 12-month treatment response to ranibizumab in patients with wet age-related macular degeneration. Am J Ophthalmol 2015; 160:1014–1023.e2.
20. Kumar N, Marsiglia M, Mrejen S, et al. Visual and anatomical outcomes of intravitreal aflibercept in eyes with persistent subfoveal fluid despite previous treatments with ranibizumab in patients with neovascular age-related macular degeneration. Retina 2013;33:1605–1612.
21. Chan CK, Jain A, Sadda S, Varshney N. Optical coherence tomographic and visual results at six months after transitioning to aflibercept for patients on prior ranibizumab or bevacizumab treatment for exudative age-related macular degeneration (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2014;112:160–198.
22. Dirani A, Ambresin A, Marchionno L, et al. Factors influencing the treatment response of pigment epithelium detachment in age-related macular degeneration. Am J Ophthalmol 2015; 160:732–738.e2.
23. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012;119:2537–2548.
24. Mariani A, Deli A, Ambresin A, Mantel I. Characteristics of eyes with secondary loss of visual acuity receiving variable dosing ranibizumab for neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2011;249: 1635–1642.
25. Introini U, Torres Gimeno A, Scotti F, et al. Vascularized retinal pigment epithelial detachment in age-related macular degeneration: treatment and RPE tear incidence. Graefes Arch Clin Exp Ophthalmol 2012;250:1283–1292.
26. Bolz M, Michels S, Geitzenauer W, et al. Effect of systemic bevacizumab therapy on retinal pigment epithelial detachment. Br J Ophthalmol 2007;91:785–789.
27. Baba T, Kitahashi M, Kubota-Taniai M, et al. Two-year course of subfoveal pigment epithelial detachment in eyes with age-related macular degeneration and visual acuity better than 20/40. Ophthalmologica 2012;228:102–109.
28. Suzuki M, Nagai N, Izumi-Nagai K, et al. Predictive factors for non-response to intravitreal ranibizumab treatment in age-related macular degeneration. Br J Ophthalmol 2014;98: 1186–1191.
29. Penha FM, Gregori G, Garcia Filho CA, et al. Quantitative changes in retinal pigment epithelial detachments as a predictor for retreatment with anti-VEGF therapy. Retina 2013;33:459–466.
30. Ho J, Adhi M, Baumal C, et al. Agreement and reproducibility of retinal pigment epithelial detachment volumetric measurements through optical coherence tomography. Retina 2015;35: 467–472.